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High-Pressure Fibrin Sealant Foam: An Effective Hemostatic Agent for Treating Severe Parenchymal Hemorrhage[1]

Bijan S. Kheirabadi, Ph.D.,*,[2] Jennifer Sieber, M.S.,† Tallat Bukhari, B.S.,† Kiti Rudnicka, M.S.,† Lara A. Murcin, M.S.,† and David Tuthill, D.V.M.‡

*US Army Institute of Surgical Research, Fort Sam Houston, Texas; †American Red Cross, Holland Laboratory, Rockville, Maryland; and ‡Kent State University, Kent, Ohio

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Background. **The majority of early trauma deaths are related to uncontrolled, noncompressible, parenchymal hemorrhage from truncal injuries. The purpose of this study was to formulate a fibrin sealant foam (FSF) able to control severe parenchymal bleeding without compression or vascular control.**

Materials and methods. **FSF with high fibrinogen concentration (20 mg/mL) and low thrombin activity (5 U/mL) was prepared and pressurized by addition of liquid gas propellant. The efficacy of this foam was tested against a severe parenchymal hemorrhage, created by partial resection of liver lobes in anticoagulated rabbits (n = 7) and compared to untreated injury (n = 8) and placebo treatment (n = 7). The hemostatic efficacy of pressurized FSF (n = 8) was also compared to a commercially available liquid fibrin sealant (n = 8) and a developing dry powdered fibrin sealant product (n = 8) in the same model.**

Results. **The liver injury resulted in 122 ± 11.5 mL blood loss and death of 75% of untreated rabbits (3.2–3.4 kg) within 1 h. Treatment with placebo foam had no effect on blood loss or mortality rate. Pressurized FSF significantly reduced bleeding, resulting in 56% (P < 0.05) and 66% (P < 0.01) reduction in blood loss as compared to untreated or placebo-treated animals, respectively, and 100% survival (P = 0.008). When pressurized FSF was compared with liquid and powdered forms of fibrin sealant, only foam significantly reduced blood loss (49%, P < 0.05) and mortality rate (54%, P < 0.05) of rabbits as compared to untreated control animals (n = 9).**

Conclusion. **Biological nature, rapid preparation, coverage of large wound areas, and effective hemostatic properties make pressurized FSF an ideal candidate for treating nonoperable parenchymal injuries in damage control procedures.**

Key Words: **hemorrhage control; fibrin sealant; fibrinogen; hemostasis; animal model; hemostatic foam.**

INTRODUCTION

A major advance in hemorrhage control was the introduction of a highly concentrated liquid solution of fibrinogen and thrombin by Spangler and coworkers in 1975 [1]. Liquid fibrin sealant (FS) established hemostasis in parenchymal bleeding and demonstrated high tissue compatibility in both experimental and clinical studies [2–5]. However, the complicated and time-consuming process of reconstituting liquid FS negated its application in trauma and time-sensitive damage control operations. Twenty years later dry dressing with lyophilized FS components circumvented many of the shortcomings of the liquid product [6]. It stopped severe aortic bleeding and maintained hemostasis for up to 4 days in a survival aortotomy model in swine [7]. Dry FS dressing could not, however, control noncompressible hemorrhage. Subsequently, Holcomb and colleagues proposed the development of a hemostatic foam to treat noncompressible bleeding [8]. They hypothesized that the infusion of self-expanding fibrin sealant foam (FSF) into a body cavity via trocar would spread throughout the cavity, bind to damaged tissue, and stop bleeding from inaccessible wounds. Their FSF prototype, containing low fibrinogen and high throm-

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[2] To whom correspondence and reprint requests should be addressed at US Army Institute of Surgical Research, 3400 Rawley E. Chambers Avenue, Fort Sam Houston, TX 78234. E-mail: Bijan.Kheirabadi@CEN.AMEDD.ARMY.MIL.

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bin activity, reduced blood loss volume when sprayed directly on rat liver injuries [9]. However, later *in vitro* and *in vivo* experiments performed in a rabbit liver injury model with more profuse bleeding (unpublished data) and in kidney stab wounds in a large animal model [10] could not confirm the results in rats. Inadequate dissolution of the ingredients and rapid clotting of the foam prevented proper preparation and application of the foam on tissues. Nonetheless, the known hemostatic qualities of FS and the potential ability of foam to act as an effective dispersal agent within an intracavitary wound prompted us to further investigate this product. We developed and tested the efficacy of a pressurized version of FSF with new formulation in a severe liver hemorrhage model in anticoagulated rabbits. We then compared pressurized FSF with liquid and a powdered form of fibrin sealant.

MATERIALS AND METHODS

FS Formulation and Preparation

Vials of freeze-dried human fibrinogen and human thrombin were obtained from Baxter Healthcare Corp. (Deerfield, IL). A new FSF formulation, shown in Table 1, was developed based on a series of *in vitro* tissue adhesion tests. The foam contains a high amount of fibrinogen (20 mg/mL) and low thrombin activity (5 U activity/mL), which polymerized slowly upon reconstitution. This allowed sufficient time (~2 min) for complete dissolution of proteins and application of the foam over large bleeding areas before the polymerization was completed and clots were formed. The clotted foam also exhibited a strong tissue-binding property to rabbit liver slices.

To prepare the foam and apply to the wounds, a liquefied gas propellant was added to the reagents. Equal volumes of saline and propellant were injected into a sealed pressure-resistant bottle containing dry powdered FS. The bottle was shaken for 30 s to dissolve the ingredients and the content (an emulsion) was sprayed on tissues at a constant high pressure. The emulsion converted into smooth foam as soon as exposed to atmospheric pressure. Foam was always prepared at room temperature for the optimum reaction time and applied to bleeding tissues or liver slices that were at ~37°C temperature.

The FS dry powder was applied with the aid of compressed air using a prototype device. The liquid FS was prepared and applied according to the manufacturer's instructions. The compositions of FS dry powder and liquid are shown in Table 1. The same sources of human fibrinogen and thrombin were used for all three products (powder, liquid, and foam). The amount of fibrinogen used in preparation of each product was the same (300 mg), while other ingredients varied depending on each product's specific formulation.

TABLE 1

Composition of Fibrin Sealant Products

Components	Foam	Powder	Liquid
Human fibrinogen* (mg)	300	300	300
Human thrombin (IU)	75	1000	1000
CaCl2, $2H_2O$ (mg)	20	40	20
Human serum albumin (mg)	210	60	60
NaCl and histidine (mg)	140	140	140
Saline (mL)	15	0	6
Total volume/amount	~ 50 mL	540 mg	6 mL

* Human fibrinogen measured as clottable protein.

In Vivo Experiments

This study was approved by the Animal Care and Use Committee of the American Red Cross Holland Laboratory. Male New Zealand White rabbits, specific-pathogen-free, weighing 3.2–3.4 kg were used for this study. All animals received care in strict compliance with *The Guide for the Care and Use of Laboratory Animals.*

Two experiments were designed and conducted sequentially. In the first experiment, 22 rabbits were divided into three groups and the efficacy of FSF was tested ($n = 7$) and compared with a placebo-treatment ($n = 7$) and no-treatment group ($n = 8$). In the second experiment, 33 rabbits were divided into four groups and the efficacy of the foam ($n = 8$) was compared with powdered ($n = 8$) and liquid forms of fibrin sealant ($n = 8$). An untreated group ($n = 9$) of rabbits was operated as control.

Animal Preparation

Animals were acclimated for at least 7 days and carefully checked for any preexisting disease before undergoing surgical procedures. The daily food was withdrawn from the surgical candidate on the morning of the operation. Anesthesia was induced with an intramuscular injection of 0.3 mL/kg Hypnorm (a combination of 0.2 mg/mL of fentanyl citrate and 10 mg/mL of fluanisone; Vet Drug Ltd., York, United Kingdom). A 0.2 mL blood sample drawn from the central ear artery determined the preoperative hematocrit. The marginal veins of both ears were cannulated with 22-gauge intravenous (IV) catheters for fluid and drug administration. The rabbit's body temperature was monitored with a rectal probe thermometer and maintained at 37.5 ± 0.5°C with the use of a heating pad. Surgical anesthesia was produced and maintained by intermittent IV infusions of 0.2–0.3 mL of 2% sodium methohexital (Brevital) solution. Oxygen was provided to rabbits at a rate of 1 L/min via a loose-fitting facemask.

Surgical Procedures

The left carotid artery was cannulated using PE-50 tubing and attached to a precalibrated pressure transducer. During the experiment, systolic, diastolic, and mean arterial pressure (MAP) and heart rate were continuously monitored and the data were collected by a computer for future analysis. A ventral midline incision approximately 20 cm long was made, and bleeding was controlled by electrocautery. Rabbits were hydrated with 10 mL/kg of lactated Ringer's (LR) solution supplemented with 2 mL sodium bicarbonate (8.4%) via IV drip during initial procedures. Following hydration, baseline MAP was recorded and rabbits were injected IV with ~0.12 mL of danaparoid sodium (150 anti-Xa units) 5 min before liver injury. To create the injury and hemorrhage, approximately 30% of the length of the middle, left, and right frontal lobes of the liver were marked (Fig. 1A) and cut sharply with scissors (Fig. 1B). If the injury and bleeding did not cause a 10% drop in MAP within 60 s, additional tissue slices of 2 mm thickness were cut from the liver lobes to ensure severe bleeding.

Within 2 min of injury, the bleeding liver surfaces were sprayed and covered with the foam, liquid, or powdered FS. In control groups, bleeding was either allowed without any intervention (untreated) or treated by spraying the injuries with a placebo foam. The placebo foam was prepared by replacing the active components of the FSF (fibrinogen, thrombin, and albumin) with an equal amount of lyophilized human IgG protein. The abdomen was then closed and the excised liver pieces were collected and weighed. Animals were then resuscitated with LR solution to return their MAP to baseline level. A maximum of 50 mL/kg of LR solution at a constant rate of 1 mL/kg/min was administered. Rabbits were monitored for 1 h after liver injury or until death. At the conclusion of the experiment, the abdomen was reopened and shed blood and blood clots, free or em-

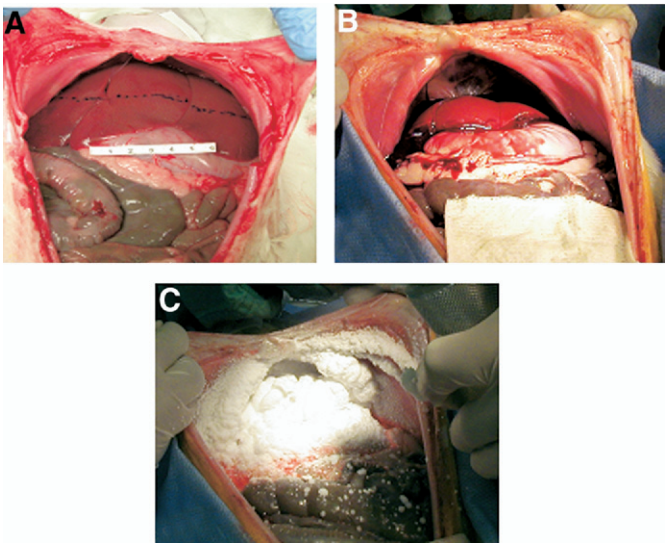

FIG. 1. Photographs of rabbit liver lobes marked before injury (A), after the resection injury (B), and after FSF treatment (C). Note the blood pools adjacent to the diaphragm shortly after the injury in (B).

bedded in the foam, were collected with gauze and weighed to estimate total blood loss. The specific gravity of blood was assumed to be equal to 1.0 g/cm^3. The injured liver was then recovered from the body and weighed to determine the percentage of the liver mass that was excised in each experiment. The surviving rabbits were exsanguinated under deep anesthesia.

Statistical Analysis

The primary endpoints of this study were the incidence of survival and hemorrhage volume. Data were analyzed with the statistical methods of the GraphPad Prizm system and expressed as means ± SEM. Kruskal–Wallis test (a nonparametric analysis of variance) was used for comparing the medians of experimental groups. Dunnett's multiple comparison test was performed for the post nonparametric analysis of variance test to compare pairs of group means. The incidence of survival was compared using Fisher's Exact test. Statistical significance was assigned at a greater than 95% confidence level ($P < 0.05$).

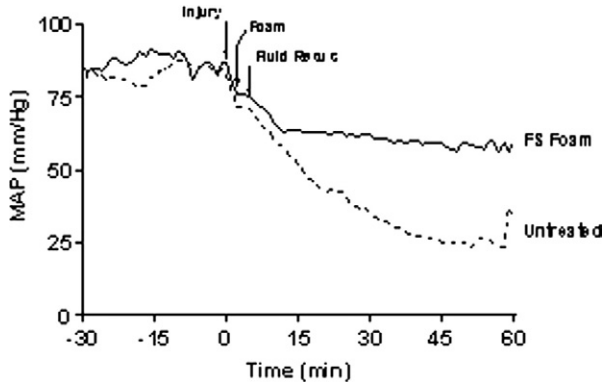

FIG. 2. The averaged mean arterial pressure (MAP) of untreated and FSF-treated rabbits during experimentation. The sudden increase of MAP in untreated rabbits at 58 min represents the blood pressures of two surviving rabbits in that group.

RESULTS

Prior to injury, the baseline MAP was 84 ± 4 mmHg with no difference between the FSF-treated and untreated groups. Approximately 17% of liver mass was excised from the frontal liver lobes to create the injury in rabbits with no difference among the groups. Following resection, the bleeding surfaces were sprayed with FSF, other agents, or left untreated, and the abdomen was closed. In untreated rabbits, the liver injury resulted in 122 ± 11.5 mL blood loss and the death of 75% of animals within 1 h of observation. Addition of liquefied propellant to the saline (main solvent) produced expanded foam that measured approximately three times the volume of the liquid material (~50 mL). This amount of foam was in excess for treating bleeding surfaces and covered almost the entire liver when sprayed (Fig. 1C). The volumes of liquid and powdered FS were sufficient to cover the entire bleeding surfaces. The fluid resuscitation (1 mL/kg/min, LR) was administered to all of the rabbits following the injury but did not exceed 50 mL/kg and the baseline MAP was not restored in any of the animals. The average MAP of rabbits treated with FSF and untreated group are shown in Fig. 2. High-pressure application of FSF on the wounds was highly effective against the parenchymal hemorrhage and significantly reduced the bleeding (Fig. 3) as compared to untreated ($P < 0.05$) or placebo-treated rabbits ($P < 0.01$). All of the treated animals also survived the hemorrhage, which was significantly higher than the control groups ($P = 0.008$). In the second experiment, spraying dry FS powder on injured liver tissues had little effect on overall blood loss. Once applied, it quickly transformed into a thin and adherent fibrin layer on contact with

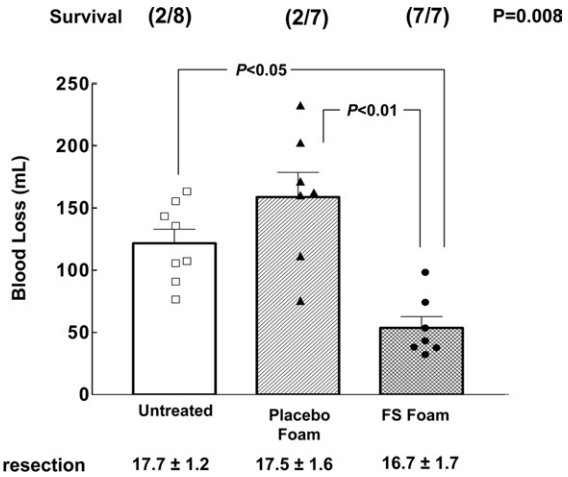

FIG. 3. Pressurized FSF treatment of liver injuries in heparinoid-treated rabbits. This treatment resulted in 56 and 66% reduction in blood loss as compared with the untreated ($P < 0.05$) and placebo-treated foam ($P < 0.01$) groups, respectively. It also improved percent survival in this group as compared with others ($P < 0.05$).

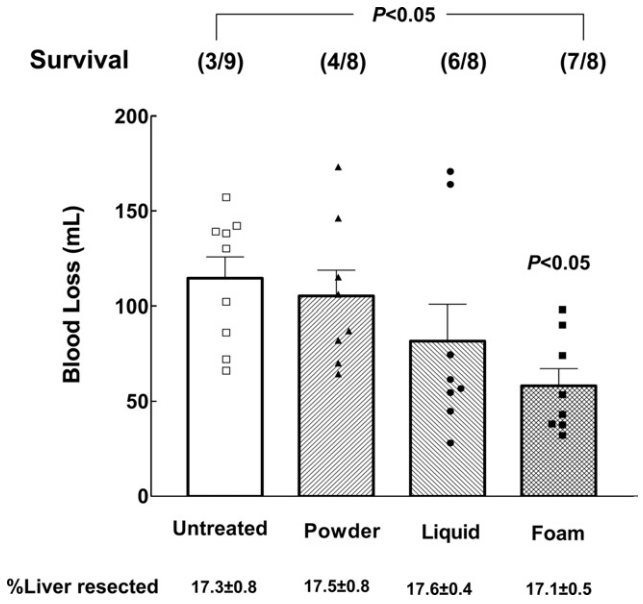

FIG. 4. Hemostatic treatment of liver injuries with different FS products in heparinoid-treated rabbits. Pressurized FSF was the most effective hemostatic treatment, reducing blood loss and improving percent survival significantly ($P < 0.05$ *versus* untreated).

slow bleeding tissue and stopped the oozing, but it was readily washed away from areas with profuse bleeding. Liquid FS was more effective than powder, but in two cases it failed to seal the profuse bleeding from transected veins. The most effective treatment was the pressurized FSF (Fig. 4). Although the differences between this group and other FS-treated animals were insignificant, only FSF application reduced blood loss and increased survival rate when compared with untreated animals ($P < 0.05$). The Kaplan–Meier survival curves also show a trend toward ($P = 0.08$) a longer survival time in FSF-treated animals as compared with other groups (Fig. 5).

DISCUSSION

The present study reports a new FSF formulation that exhibits hemostatic efficacy in a severe parenchymal bleeding model. The formulation was substantially modified from the original product tested in a rat liver injury study [9] to contain a high concentration of fibrinogen, which strengthened the tissue-binding properties of fibrin, and low thrombin activity and $CaCl_2$, which reduced the clotting rate of the fibrinogen, allowing sufficient time to reconstitute and apply the product efficiently. Unlike liquid FS, the foam requires less than 1 min for preparation and can be dispensed instantly to control active parenchymal bleeding without vascular control.

Uncontrolled hemorrhage accounts for 39% of trauma-related deaths and is the leading cause of potentially preventable death in patients with major trauma [11, 12]. While bleeding from vascular injury can usually be repaired surgically, bleeding from parenchymal organs particularly in coagulopathic patients is often more difficult to manage. Hoyt *et al.* reported that 50% of all early civilian trauma deaths were due to uncontrolled hemorrhage caused by severe liver injuries [13]. The method most frequently used to control hemorrhage in severe liver injuries is gauze packing, which requires a second operation for removal of gauze at a later time [14]. It can also be associated with a number of complications, including rebleeding after pack removal [15], abdominal compartment syndrome [16], and increased incidence of sepsis [17]. The use of a hemostatic product like FSF may be extremely beneficial in such a situation, providing rapid hemostasis and eliminating the need for additional operation and other complications. In cases of damage control operations, particularly in the coagulopathic patient, spraying a hemostatic foam can stop diffuse bleeding from multiple injury sites and unmask major vascular injuries that require surgical repair. It may also have a potential utility in laparoscopic surgeries if the safety and technical difficulties of the application can be overcome.

The wide area application of FSF in the peritoneal cavity may suggest a potential risk for FSF to cause tissue adhesion. However, no significant complication was found when severe liver injuries were repaired with FS dressing and pigs were monitored for 14 days [18]. Also, in a recent study in which an aortotomy injury was repaired for FS dressing and animals were monitored up to 8 weeks, no significant tissue adhesion was found in the peritoneal cavity [19]. Given the low density of fibrin clot in the foam, it is likely that the foam is degraded and reabsorbed more rapidly than FS dressing without causing tissue adhesion.

The efficacy of pressurized FSF was found to be superior to other FS products when compared with bleeding in untreated animals. Application of FSF with

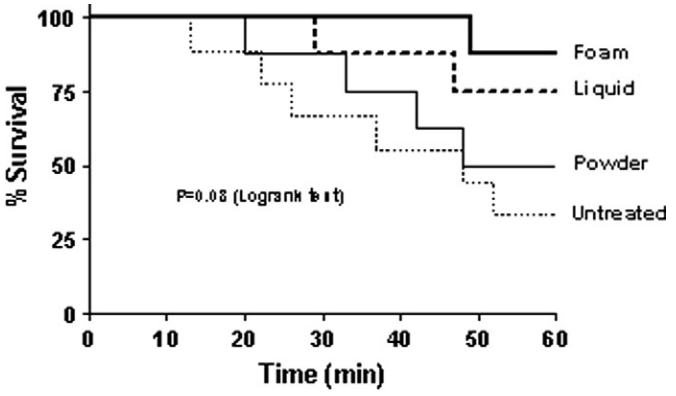

FIG. 5. Kaplan–Meier survival curves of rabbits following liver injuries and treatment with different FS products. The high-pressure FSF-treated rabbits showed a trend toward longer survival time ($P = 0.08$) than the other groups.

high-pressure propellant displaced the pooled blood in the wound and momentarily stopped the bleeding from the transected veins. This allowed better contact and stronger bonding between fibrin clot and the injured tissues than when other FS products were used for treatment. Application of FSF to the wounds without propellant had only a marginal effect in decreasing blood loss (preliminary data). The high thrombin activity in the dry and liquid products did not add to the hemostatic efficacy of these agents in this model. The predominant mechanism by which the FS products produced hemostasis in this model appeared to be through tissue binding and sealing of the bleeding sources, rather than by promoting natural blood clotting at the injury site. This is perhaps the reason this hemostatic agent, unlike any other, is effective in controlling the surgical bleeding even in hemophiliac patients [20, 21].

To evaluate the hemostatic efficacy of the newly formulated FSF, we developed a new parenchymal hemorrhage model in the rabbit. Our objective was not only to demonstrate that FS foam can reduce the blood loss, but also to prove that this treatment will delay or prevent mortality. The rat model in the original FS foam study [9] was not considered because the demonstrated reduction in blood loss in that model did not correspond to deceases in mortality rate. After performing a series of model development experiments, we concluded that, because of anatomical variation and hemostatic differences in normal rabbits, it appears to be impossible to create a consistent liver injury that would cause reproducible bleeding and high mortality in animals but also provide an opportunity for treating the injury and improving the outcome. Therefore, treatment with an anticoagulant (heparin, 200 U/kg, IV) prior to injury was incorporated in the model. Heparin has been used to enhance the bleeding in other hemorrhage models involving vena cava or parenchymal organ injuries when the efficacy of a new hemostatic agent or method was tested [22–25]. In our preliminary experiments, heparinization consistently produced high blood loss (>150 mL) and 100% mortality, but also prevented any hemostatic interaction of FSF with the tissues. It appeared that heparin's thrombin inhibition function affected the thrombin enzymatic activity and fibrinogen polymerization in the FSF. This observation contradicted many reports that claim liquid FS is efficacious even in heparinized subjects [26–28]. However, the liquid FS used in those studies contained 100- to 150-fold higher thrombin activity than the FSF preparation tested here. Furthermore, in most situations where FS was used as a hemostatic adjuvant (e.g., vascular surgery), bleeding was temporarily controlled by clamping and removing heparinized blood from the surgical field before FS was applied [29, 30]. In contrast, in our model foam was applied to tissue covered with heparinized blood while uncontrolled bleeding continued. The limitations of the hemostatic effectiveness of liquid FS to control high-pressure bleeding under conditions of systemic heparinization have been reported elsewhere [31, 32].

Thus, a new class of anticoagulant, heparinoid, was selected and tested in the model. The anticoagulant activity of heparinoid is predominantly due to the inhibition of factor Xa activity in the blood and has little effect on thrombin function (heparinoid inhibition ratio of factor Xa to thrombin is 20:1). Although this anticoagulant suppressed rabbit blood clotting function, it appeared to have no effect on clotting reaction of FSF or its tissue binding property. *In vitro* tests also showed that, unlike heparin, heparinoid treatment did not interfere with the binding of FSF to liver slices covered with anticoagulated blood. A relatively high dosage of heparinoid (50 units anti factor Xa activity/kg) was injected intravenously to obtain maximum effect in the rabbits. This pretreatment produced more consistent and greater blood loss and mortality in the rabbits than those seen in untreated normal animals. When the data from three groups of rabbits (untreated, heparin, and heparinoid treated) were analyzed, the average blood loss of surviving animals (62.7 ± 8.5 mL) was significantly less than those died (130.2 ± 5.2 mL) during the experiments ($P < 0.0001$). These data suggested that the severity of hemorrhage was the main factor in determining death or survival of the rabbits. We recognized that the use of any anticoagulant compromises traumatic hemorrhage models; however, we believed that the assessment of a hemostatic agent that does not rely solely on the host's normal clotting function is valid, particularly because anticoagulation presents a greater challenge to a hemostatic agent for control of hemorrhage than normal coagulation condition.

In summary, a new formulation of FSF with a strong parenchymal tissue adhesive property was developed in our laboratory. The hemostatic efficacy of this formula was tested in a severe liver hemorrhage model that caused 75% mortality in untreated anticoagulated rabbits. Addition of a high-pressure propellant for preparation and delivery of the foam enhanced the hemostatic efficacy of the product and prevented death in 87 to 100% of animals. FSF may be more cost effective than liquid or powdered FS product since it requires less human fibrinogen and thrombin per treatment. The rapid preparation time of less than 1 min and the large volume of foam that can cover extensive bleeding areas are great advantages of this product compared with alternative FS agents. Pressurized FSF may offer a new tool for damage control surgery, particularly for treating life-threatening parenchymal bleeding of coagulopathic patients.

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